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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/509,239	03/23/2000	CLAUDINE BRUCK	B45110	3102

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SMITHKLINE BEECHAM CORPORATION
CORPORATE INTELLECTUAL PROPERTY-US, UW2220
P. O. BOX 1539
KING OF PRUSSIA, PA 19406-0939

EXAMINER
WINKLER, ULRIKE

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 09/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No. 09/509,239	Applicant(s) BRUCK ET AL.	
	Examin r Ulrike Winkler, Ph.D.	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-77* is/are pending in the application.

4a) Of the above claim(s) *55-77* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The request filed on July 3, 2002 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/509,239 is acceptable and a RCE has been established. An action on the RCE follows.

The Amendment filed April 17, 2002 (Paper No. 17) in response to the Office Action of October 22, 2001 is acknowledged and has been entered. Claims 32-77 are pending. Claims 55-77 are withdrawn from consideration as being drawn to a non-elected invention. Claims 32-54 are currently being examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Drawings

The drawing filed on January 15, 2002 have been approved by the Draftsperson.

Claim Rejections - 35 USC § 112

The rejection of claims 32, 36 and 50-54 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention **is withdrawn.** After review and reconsideration in view of applicant's arguments the issues previously raised under lack of written description are now addressed under scope of enablement (see below).

The rejection of claims 37 and 38 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention **is maintained.** The specification does not provide a written description for a lipoprotein and "immunogenic derivatives" thereof.

The rejection of claims 32-34 and 54 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention **is withdrawn** in view of applicant's amendments to the claims whereby the term "immunogenic derivative" has been deleted.

The rejection of claims 37 and 38 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention **is maintained** which still contain reference to a lipoprotein and "immunogenic derivatives" thereof.

The rejection of claims 32-34 and 54 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention **is withdrawn** for in view of applicant's amendments to the claims whereby the term "immunogenic derivative" has been deleted.

The rejection of claims 32 and 35 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention **is withdrawn** in view of applicant's amendments to the claims deleting the phrase "derivative as an immunogenic mutated Tat protein".

The rejection of claims 32 and 36 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention **is withdrawn** in view of applicant's amendments to the claims "derivative as an immunogenic mutated Nef protein".

The following new 35 U.S.C. 112, fisrt and second paragraph rejections are made:

Claims 32-54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for Nef-Tat and fusion partner-Nef-Tat as set out in SEQ ID Nos: 12, 13, 16, 17, 20, 21, 23, 24 does not reasonably provide enablement for "mutants thereof" or "immunogenic derivatives thereof".

The instant claims are evaluated for scope of enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows: (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

(1) The nature of the invention is an immunogenic fusion protein that comprises Nef and Tat sequences , "mutants thereof" or "immunogenic derivatives thereof". The

compounds of the invention are to be used as immunogens, which will provide protection against HIV infection when injected into a subject. Because the immunogens are to provide protection, conformation of the epitopes is important to achieve this function. (2) The state of the prior art is such that the methods and skills of physically making mutations within a given nucleotide sequence is well known. The ordinary artisan is capable of making insertions, deletions or additions of single or multiple nucleotides at any point within a known nucleotide sequence. The specification describes the following Tat mutations Lys 41→ Ala, Arg 78→ Lys and Asp 80→ Glu the specification does not describe how these mutations affect the immunogenic character of Tat, let along the Nef-Tat fusion. (3) The art lacks predictability in making mutations that will result in a desired outcome of being immunogenic and providing a protective effect [see Corchero et al. Antigenicity of a viral peptide displayed on beta-galactosidase fusion protein is influenced by the presence of the homologues partner protein. FEMS Microbiology Letters (1996) Vol. 145., pp. 77-82; Abaza et al. Effects of amino acids substitutions outside an antigenic site on protein binding to monoclonal antibodies of predetermined specificity obtained by peptide immunization. Journal of Protein Chemistry (1992) Vol. 11, No. 5, pp. 433-444]. Cochero et al. discloses that the antigenic site can display different antigenicity depending on the global construction of the chimeric protein that contains VP1. Long distance influences occurring in the fusion protein can also determine the antigenic behavior of a small peptide exposed in its natural framework (see Corchero et al. last paragraph). (4) The amount of direction or guidance present in the specification is insufficient to allow the ordinary artisan to make mutations in the sequences and be able to determine at what point the mutations in the sequences of Tat or Nef will fall outside the claimed immunogenic composition or "mutant

thereof" or "immunogenic derivatives thereof". The specification does not provide any limits as to the amount of mutations, hence every single amino acid in the sequence can be mutated or deleted or inserted, in essence at the end a completely different molecule can be made that looks nothing like the original Nef or Tat protein. The specification provides no measurable function that can be used as a guide when making "mutants thereof" or "immunogenic derivatives thereof". For example if one has a an enzyme that is able to catalyze a substrate at a given rate, the ordinary artisan could then make mutations in the enzyme coding sequence and compare the activity of the mutant to the normal enzyme using the substrate. If the mutant cannot catalyze substrate the ordinary artisan would know that this mutant is not functional and could not be considered a mutant thereof. Another method of linking structure with function is to have identified a critical epitope in a protein, the ordinary artisan could them make mutations in the protein and determine the functionality as based on binding of an antibody to the specific epitope (see Corchero et al. FEMS Microbiology Letters (1996); Abaza et al.. Journal of Protein Chemistry (1992). The disclosure of a single mutant (SEQ ID 23) is not satisfactory as a point of comparison because the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g. see Ngo et al., (V), newly cited, in The Protein Folding Problem and Tertiary Structure Prediction,1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.), it would require an undue amount of experimentation for one of skill in the art to arrive at the other amino acid sequences that have the desired activity of conferring protection on a subject. (5) The presence or absence of working examples, the specification has provided only a single exampel of a Nef-Tat mutant (SEQ ID 23) this single example does not provide sufficient guidance as the correlation between

peptide and the tertiary structure are not predicable. There is insufficient guidance in the specification to allow the ordinary artisan to make the "mutants thereof" or "immunogenic derivatives thereof" so that they retain the desired activity of conferring protection on a subject. (6) The quantity of experimentation is high and although some experimentation is permissible in this instance there is no clear assay or method for determining which "mutants thereof" or "immunogenic derivatives thereof" will have the desired immunogenic character that will provide protection in a subject. (7) The relative skill of those in the art is high and (8) the breadth of the claims are such that an indefinite number of mutations (insertions, deletions or substitutions) can be made, yet the ordinary artisan would not know how to determine the structure of the requisite fusion proteins and "mutants thereof". Because there are no structural limits provided in the specification as to the required core structure it is impossible to determine when a peptide is a mutant of Nef or Tat and when it is not. Therefore, the instant invention is not enabled for the full scope of the claim.

Claims 32-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is rejected because it is not clear if applicant is intending a particular order of the Nef-Tat or Tat-Nef orientation in claim 32. Claim 32 (a) which is drawn to an HIV Tat or mutant thereof linked to HIV Nef or mutant thereof. There is no indication in this part (a) of the claim that would limit the structure to Tat-Nef only it could as easily be Nef-Tat, the term "linked to" does not provide any indication as to the structural orientation of the fusion protein of the claim. Therefore, it is not clear if something different is intended in claim 32 (b) is drawn to

an HIV Nef or mutant thereof linked to HIV Tat or mutant thereof, again this part of the claim does not provide any indication as to the preferred orientation. Because there are no structural difference between part (a) and (b) of claim 32 the claim is indefinite because it is not clear if part (b) is just a duplication of part (a) and in that instance should be deleted; or if applicant intended part (b) to have different structure from part (a), if that is the case applicant needs to amend the claim to clarify what the structural difference are between part (a) and part (b) of the claim.

Claim Rejections - 35 USC § 103

The rejection of claims 32-54 under 35 U.S.C. 103(a) as being unpatentable over Schluesener (Journal of Neuroscience 1996, found on 892 of paper No. 4) and Hinkula et al. (Journal of Virology 1997), claim 35 further in view of Gaynor et al. (U.S, Pat. No. 5,597,895), claims 50-53 further in view of Berman et al. (U.S. Pat No. 5,864,027) or claims 37-39 further in view of Forsgren (U.S. Pat. No. 5,888,517) **is maintained** for reasons of record.

Applicants arguments are that the references do not use Tat the fusion peptide to provide protection against HIV, and that the references does not indicate that a Tat fusion protein would provide a protective vaccine. Applicant argues that the Schlusener et al. reference does not require Tat to be an immunogenic component, and that Tat is used only as delivery vehicle. Applicant further argues that neither of the primary references teaches a combination of two full length proteins in a fusion state. Applicant argues that one of the references teaches a DNA approach while the other reference teaches a peptide approach, in essence applicant argues that there is no suggestion to combine the references. However, injecting a plasmid into an animal

will produce a protein to which the animal amounts an immune response. It is the protein to which the antibodies are directed and not the DNA. Therefore, the argument that different approaches are being used is not convincing, as the end result is an immunogenic reaction.

Applicant's arguments filed July 3, 2002 have been fully considered but they are not persuasive. In response to applicant's argument that there is no suggestion to combine the references, because the references teach different approaches, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, each of the references teaches a composition and each of the compositions are used for the purpose of immunization to elicit an immune response in a subject.

Further, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the construct provide protection against HIV, protective vaccine) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The instant invention is drawn to a composition comprising an HIV Tat and Nef protein or "mutant thereof" linked to each other or a Tat – Nef fusion protein linked to another "immunogenic protein thereof", such as *H. influenza* lipoproteins. In addition, the immunogenic

composition comprises HIV gp-160 or derivative thereof as well. The composition is immunogenic, any peptide greater than 6 contiguous amino acids will be immunogenic when injected into an animal. The immunogenic character does not require that the protein also be prophylactic. The specification defines a "mutant" (page 3, lines 6-9) as a molecule which has undergone deletion, addition or substitution of one or more amino acids using well known techniques.

Schluesener teach a composition of a polyvalent Tat peptide as an immunogen. The reference teaches linking HIV Tat to three pathogenic T-cell epitopes, this fusion combination to HIV Tat improves their immunogenicity. The Tat is used as "targeting tool" to improve the cellular uptake the fusion peptide. Tat is 40 amino acids in length, far greater than the minimum 6 amino acids required to produce an immune response. Therefore, based on what is known in the art the Tat protein linked to pathogenic T-cell epitopes will also be presented to the immune system so that antibodies may be made against it. Therefore, the peptide is immunogenic as required by the instant invention. This reference does not teach a DNA approach as suggested in applicant response. The reference clearly teaches using Tat to improve cellular uptake of the linked epitope and cellular uptake will lead to more efficient presentation of the epitopes to the cells of the immune system. The reference does not explicitly teach immunizing with Nef. However, since there are no limits as to the amount of mutation substitution or deletion that may be made in the Nef protein and the resultant molecule may look nothing like Nef, the T-cell epitopes fused to Tat could be "mutants of Nef".

Hinkula et al. teach a composition comprising Nef, Tat or Rev as an immunogen. The reference teaches that an immune response to the regulatory proteins of HIV is an important

response in formulating protection. Animals produce both cellular and humeral responses to these regulatory proteins. The plasmids used for the induction of an immune response comprise coding sequences for *nef, tat, rev, gag* and *gp160*, these plasmids are used in a single composition for immunization. The reference suggests that due to the polymorphism found in the human population, an effective vaccine will require the combination of many proteins or glycoproteins (page 5538 last paragraph). The reference teaches a composition comprising all the regulatory genes and well as the structural genes for the envelope gp160 and gag for the immunization of an animal (see abstract). The reference teaches immunizations with DNA that will translate into full length protein Tat or Nef sequences to which the animals mount a humoral immune response. The reference also teaches immunization with full length recombinant proteins Nef, Tat and Rev which are used for comparison with the plasmid immunizations (see protein immunization, column 1, page 5529). The protein immunizations are carried out with either Freund's adjuvant (which are killed mycobacteria in an oil in water emulsion) or Ribi adjuvant (an oil and water emulsion containing detoxified endotoxin and mycobacterial cell wall components). The reference does not teach a Tat-Nef fusion protein.

Gaynor et al. teach the production of Tat mutants. In the reference the Tat mutants are assayed for their ability to inhibit HIV gene expression. The wild type and mutant Tat proteins are produced as a fusion protein with a sequence (15 amino acids) from the influenza haemagglutinin protein (column 22, line 50 to column 23, line 3). The influenza haemagglutinin protein serves an en epitope tag for affinity purification of the Tat and mutant Tat proteins. Although the fusion protein was not used in assays to determine the ability to elicit an immune

response the fusion proteins are of sufficient size to elicit an immune response in a subject. The reference does not teach a Tat-Nef fusion protein.

Berman et al. teach the composition comprising HIV env, gp120 fragments as immunogenic compositions. Here chimpanzees are immunized with gp120 and later challenged with an infectious dose of HIV (see U.S. Pat No. 5,864,027, column 53 lines54-64). The reference does not teach using the gp120 protein in conjunction with a Nef-Tat fusion protein as an immunogen.

Forsgren teach *H. influenza* lipoprotein D fusion protein as an immunogenic composition (see claim 5). The reference teaches the isolation and purification of protein D and the use of protein D as an immunogen. The reference does not teach coupling a Tat-Nef construct with protein D as a fusion protein.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to formulate a polyvalent immunogen using multivalent linked/fused HIV antigens (as taught by Schluesener) as well as multiple HIV antigens (as taught by Hinkula et al.) to stimulate immune responses to HIV. The ordinary artisan would have been motivated to provide many different peptides which can be efficiently taken up by cells in order to maximize the immune response against the pathogen. One of ordinary skill in the art at the time the invention was made would have been motivated to fuse the HIV Tat and Nef that is to be used as an immunogen following the teachings of Hinkula et al. which indicate that a successful vaccine/immunogen will require many proteins. Hinkula et al. teach a composition comprising the full length Nef, Rev, Tat, gp160 and gag in a single formulation for the injection into an animal. It would also been obvious to the ordinary artisan that when constructing the fusion

protein containing many epitopes to additionally add an epitope tag (such as histidine or GST) for purposes of purification which would simplify the production of the immunogen, the motivation being the simplified procedure (see also Gaynor et al. Tat fusion with influenza tag). The references of Gaynor et al., Berman et al. or Forsgren teach the additional limitations in view of the primary references Schluesener and Hinkula et al. It is *prima facie* obvious to combine two compositions each of which is taught by prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose; the idea of combining them flows logically from their having been individually taught in prior art. *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06. Optimizing the formulation of the composition (specifically claims 43- 49), including the addition of adjuvants or protein modification (carboxymethylation) or denaturation agents fall within the skill of an ordinary artisan. If the addition of the modulating compounds produces an unexpected result, applicant needs to point out what the unexpected results are.

Therefore, the instant invention of claims 32- 54 are obvious over Schluesener and Hinkula et al. further in view of Gaynor or Berman et al. or Forsgren.

Conclusion

Claims 32-54 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ulrike Winkler, Ph.D. 9/9/02